Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope

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All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Key words: Brugada syndrome; syncope; electrophysiological study; risk stratification; ICD; loop recorder.

Abstract

Background. Syncope is considered a risk factor for life-threatening arrhythmias in Brugada patients. Distinguishing a benign syncope from one due to ventricular arrhythmias is often difficult, unless an ECG is recorded during the episode. Aim of the study was to analyze the characteristics of syncopal episodes in a large population of Brugada patients and evaluate the role of electrophysiological study (EPS) and the prognosis in the different subgroups.

Methods and results. One hundred ninety-five Brugada patients with history of syncope were considered. Syncope were classified as neurally mediated (group 1, 61%) or unexplained (group 2, 39%) on the basis of personal and family history, clinical features, triggers, situations, associated signs, concomitant therapy. Most patients underwent EPS; they received ICD or implantable loop-recorder on the basis of the result of investigations and physician's judgment. At 62±45 months of mean follow-up, group 1 showed a significantly lower incidence of arrhythmic events (2%) as compared to group 2 (9%, $p<0.001$). Group 2 patients with positive EPS showed the highest risk of arrhythmic events (27%). No ventricular events occurred in subjects with negative EPS.

Conclusion. Etiological definition of syncope in Brugada patients is important, as it allows identifying two groups with different outcome. Patients with unexplained syncope and ventricular fibrillation induced at EPS have the highest risk of arrhythmic events. Patients presenting with neurally mediated syncope showed a prognosis similar to that of the asymptomatic and the role of EPS in this group is unproven.

Introduction

Brugada syndrome is a genetic arrhythmogenic disease characterized by coved type ST-segment elevation in at least one right precordial lead, associated with an increased risk of ventricular arrhythmias, which can cause syncope and sudden death also as first manifestation.[1-3] All the studies on risk stratification in patients with Brugada ECG pattern agree in considering syncope as a risk factor for life-threatening arrhythmias.[3-9] Differentiation of syncope due to vagal response or orthostatic hypotension, which are the most frequent causes of syncope in the general population,[10] from syncopal episodes due to ventricular arrhythmias is often difficult in Brugada patients, unless an ECG is recorded during the episode. Indeed, vagal nerve activation in these subjects can both cause neurally mediated syncope and act as trigger for ventricular fibrillation (VF).[11] Determination of the etiology of syncope is important to identify the patients who require an implantable cardioverter-defibrillator (ICD). However, few studies have focused on the etiological differentiation of syncope in Brugada patients.[12-14]

Aim of this study was to analyze the characteristics of syncopal episodes in the patients of the Brugada Registry of the Piedmont Region of Italy, by considering two groups with different probability of arrhythmic syncope, on the basis of history, clinical features, situations and results of the investigations performed. The role of electrophysiological study (EPS) and the long-term prognosis in the two groups was also evaluated.

Methods

Study population

Consecutive patients with spontaneous or drug-induced Brugada ECG pattern were prospectively collected in the Brugada Registry of the Piedmont Region in Italy, from 2001 to 2014. More than 90% of the Cardiology Divisions in the Region with an

electrophysiological laboratory participated in the study. The study was approved by the Medical Ethical Committee of our Institution. Diagnosis of Brugada ECG pattern was established according to the Consensus Conference criteria[1,2] and, since 2013, according to HRS/EHRA/APHRS expert Consensus statement.[3]

The 825 patients in the Brugada Registry were classified according to the symptoms reported at the first clinical observation as: subjects with sudden death or aborted sudden death (22; 2%), subjects with syncope (195; 24%) and asymptomatic (608; 74%). Only patients with history of syncopal episodes, occurred at or before the inclusion in the Brugada Registry, were considered in this study. We splitted the 195 patients with syncope in two study cohorts on the basis of the nature of the experienced syncope: neurally mediated (group 1) or unexplained (group 2). Sixty-two of these patients were already included in the FINGER study,[8] 67 in a study by Delise et al.[15] and 3 in the PRELUDE study[9].

Definition of syncope and data collection

Syncope was defined as transient loss of consciousness with spontaneous recovery, without neurological impairment.[16]

Diagnosis of neurally mediated syncope was made in the presence of orthostatic hypotension (defined as described in the ESC guidelines on syncope[15]) or highly likely vaso-vagal syncope (≥1 typical prodromes, ≥1 typical triggers or situations - see Table 1B - and/or positive HUTT and absence of severe physical injuries). Syncope was considered of unexplained origin in the absence of the above-mentioned conditions (absent or brief prodromes, absence of specific triggering circumstances, loss of consciousness <1 minute, and fast return to consciousness),[13] particularly when occurring during fever or after administration of contraindicated drugs (www.brugadadrugs.org) and in case of physical

injuries due to syncope. In case of multiple syncopal episodes the diagnosis was based on the characteristics of the most severe one. Syncopal episodes were analyzed collegially by three physicians; in case of uncertainty, the classification was established by agreement. Patients were seen at the outpatient clinic or interviewed by telephone and questioned about personal and family history and about the syncopal event, as suggested by ESC guidelines on syncope.[15] In each subject we investigated the number of previous syncope, triggers, situations, prodromes, associated signs (incontinence, convulsions, agonal respiration) and duration of the loss of consciousness. We got information about other diseases, presence of autonomic neuropathy and medications. A family history of sudden unexplained death at age <45 years was recorded. Data on the occurrence of injury as a result of the syncope were collected. Patients underwent 12-lead 24-hour Holter monitoring, exercise test and head-up tilt test (HUTT), based on the physician's choice. HUTT was performed, according to the ESC guidelines.[15]

The presence of an underlying structural heart disease was ruled out through physical examination and echocardiography. PR interval was measured in lead II on the basal ECG. A genetic test, searching for mutations in SCN5A and SCN1B genes, was proposed to the patients with spontaneous type 1 ECG or familial Brugada ECG pattern.

Electrophysiological study

In the Piedmont Brugada Registry, until 2009, EPS was recommended to all the patients with spontaneous or drug-induced Brugada ECG pattern; thereafter, we no longer indicated EPS in asymptomatic patients without spontaneous type 1 ECG, but we continued to propose EPS to all the subjects with spontaneous type 1 ECG, even asymptomatic, and to the patients with unexplained syncope with or without spontaneous type 1 ECG[7]. After obtaining informed written consent, EPS was performed mainly according to a protocol

with a maximum of 2 ventricular extrastimuli, from 2 ventricular sites (apex and right ventricular outflow tract), at 2 different pacing cycle lengths (600 and 400 ms); extrastimuli were anticipated in 10 ms decrements up to 160 ms or to the shortest coupling interval which resulted in ventricular capture. Alternatively, the PRELUDE protocol was applied.[9] EPS was considered positive if sustained ventricular arrhythmias (VF, polymorphic ventricular tachycardia (VT) or monomorphic VT lasting > 30 seconds or requiring emergency intervention) were induced.

Device implantation and follow-up

Patients received ICD or implantable loop recorder (ILR) on the basis of results of the investigations and clinical judgment. ICD were programmed with a single VF zone above 210-220 bpm and a detection time of 18/24 cycles or 2 seconds. Patients with ICD were followed in the ICD clinic of the referring Center every 6 months. Data from ILR were transmitted and analyzed every month. Patients were considered to have an arrhythmic event at follow-up if VF or sustained VT were documented or sudden death (SD) or appropriate ICD shock (delivered for VF or VT) had occurred. Inappropriate shocks were defined as those delivered in the absence of ventricular arrhythmias. Patients without implantable devices were seen at the outpatient clinic of the referring Center at least once a year and the data sent to the Brugada Registry. Follow-up of patients receiving hydroquinidine was stopped at the beginning of the treatment.

Statistical Analysis

Continuous variables satisfied the Shapiro-Wilks normality test and are presented as mean ± standard deviation, and compared with the non-parametric Mann–Whitney test. Dichotomic variables are presented as number and percentages and compared with the chi-square test with Yates' correction or Fisher's test when more appropriate. Freedom

from adverse events during the follow-up years is represented by the Kaplan-Meier curves and compared with the Mantel-Cox test. All tests were two-sided and statistical significance was defined as $p \leq 0.05$. All calculations were performed using SPSS 20 (IBM, Armonk, NY, USA).

Results

We focused on the 195 patients with history of syncope. Mean age at the inclusion in the Brugada Registry was 44±14 years; 146 patients (75%) were males. Ninety-seven subjects (50%) had spontaneous type 1 ECG. Mean PR interval was 178±30 ms. Genetic analysis was performed in 83 (43%) and mutations in SCN5A or SCN1B genes were found in 26 (31%). PR interval was 199±40 ms in patients with SCN5A mutation and 179±29 ms in those without mutation, ($p<0.001$). Mean age at the first syncopal episode was 35±16 years (range 2-68).

Baseline characteristics of the two groups

Table 1A and 1B show the clinical characteristics of the 2 groups. Neurally mediated syncope (group 1) occurred in 118 out of 195 patients (61%). The remaining 77 patients (39%) had unexplained syncope (group 2). Mean age at the first syncope was 33±16 and 36±15 respectively; mean time from 1st syncope to the inclusion in the Registry was 12±14 years in group 1 and 7±11 years in group 2, $p=0.02$. Mean number of syncopal episodes before diagnosis was 2.0±1.5 in group 1 and 1.6±1.3 in group 2 (p=NS).

As expected, in group 1 there was a higher prevalence of prodromes as compared to group 2. Cough, micturition, venipuncture, sight of blood or intense pain were situations predictive of neurally mediated syncope. At the opposite, loss of consciousness during driving and trauma occurred more often in group 2.

Group 2 showed a significantly higher prevalence of spontaneous type 1 ECG as compared to group 1 ($p<0.001$). The rate of subjects with genetic mutation was not different between the two groups. Mean PR interval was significantly longer in group 1 than in group 2 ($p<0.001$).

Electrophysiological study: protocol of stimulation

One hundred twenty-eight patients underwent EPS, in 99 (77%) with a maximum of 2 extrastimuli and 29 (23%) with up to 3 extrastimuli. In the first group (2 extrastimuli), 30 (30%) had sustained arrhythmias induced and 6 (20%) had arrhythmic events at follow-up. In the second group (3 extrastimuli), 14 (48%) had sustained ventricular arrhythmias induced and 3 (15%) had events at follow-up. The rate of VF induction was not statistically different between the two protocols and there was no difference in the rate of events at follow-up between the patients induced with one protocol or the other (20% *vs* 15%). The rate of VF induction at EPS was not significantly higher in patients with spontaneous type 1 (35/78, 45%) as compared to those with drug-induced type 1 (15/50, 30%, p= NS).

Electrophysiological study in the two groups and device implantation

Seventy-one patients (60%) in group 1 and 57 (74%) in group 2 underwent EPS (p=NS): VF was induced in 34% and 46% of subjects, respectively (p=NS).

Subcutaneous loop-recorder was implanted in 11% of patients in group 1 and 18% in group 2. Sixty-seven patients (34%) received an ICD, 23 (19%) in group 1 and 44 (57%) in group 2 ($p<0.001$).

In Group 1, 3 patients had an ICD implanted despite a negative EPS, following the patient/physician preference. On the other hand, in group 1, 3 patients with a positive EPS refused ICD implant. In group 2, 5 patients did not undergo EPS study, nor were they implanted an ICD. Four of them refused both EPS and ICD implantation, the other one was a

3 years old child with syncope and type 1 ECG during fever: a loop recorder and hydroquinidine therapy were proposed, but were refused by the parents.

Follow-up

During a mean follow-up of 62±45 months, 2 arrhythmic events occurred in the group with neurally mediated syncope (group 1) and 7 in the group with unexplained syncope (group 2). The event rate at follow-up was significantly higher in group 2 (9%, 1.8 per 100 person-year) as compared to group 1 (2%, 0.3 per 100 person-year; p=0.04, RR= 5.4, 95%CI: 1.1-25.1). Figure 1 shows the Kaplan Meier curves for the probability of freedom from arrhythmic events for the two cohorts and for the asymptomatic patients of the Piedmont Brugada Registry.

Details on the patients with arrhythmic events.

Table 2 summarizes the characteristics of patients with and without arrhythmic events in the two groups.

Mean age at first ICD intervention was 46±7 in group 1 and 44±14 years in group 2 (p=NS); the average time elapsed since the last syncope to the documented arrhythmic event was 5±7 years in group 1 and 5±4 years in group 2.

Of the 2 patients with arrhythmic events at follow-up in group 1, one had history of recurrent syncope after meals, preceded by nausea and malaise, interpreted as vaso-vagal. Carotid sinus massage was positive. He underwent ICD implant, because of spontaneous type 1 ECG pattern and positive EPS. After a 4-month follow-up, he had recurrence of syncope after meal with the usual prodromes and palpitation: ICD interrogation showed an episode of polymorphic VT interrupted by shock. The other patient had an episode of syncope while standing, preceded by dizziness and blurring vision and had a positive

HUTT. He underwent ICD implantation after a positive EPS and experienced an appropriate ICD shock nine years after, preceded by dizziness but without loss of consciousness.

ECG pattern

In group 1, one arrhythmic event occurred at follow-up among the 46 subjects with spontaneous type 1 ECG pattern (2%) and one among the 72 subjects with drug-induced type 1 (1%); in group 2, 6 out of 51 patients with spontaneous type 1 ECG (12%) and 1 out of the 26 with drug-induced type 1 (4%) had arrhythmic events. As shown in Table 2, there was no statistically significant difference between patients with spontaneous and drug-induced type 1.

Electrophysiological study

Inducibility of VF at EPS was a significant predictor of ventricular arrhythmic events at-follow-up. There were no ventricular arrhythmic events at follow-up in the 78 subjects with negative EPS, while all the 9 events occurred in the 50 subjects with positive EPS (18%, 3.5 per 100 person-year; $p<0.001$). EPS showed sensitivity of 100%, specificity of 66%, positive and negative predictive value of 18% and 100% respectively, in identifying patients with arrhythmic events. When adjusting this result by the baseline ECG pattern, in the patients with spontaneous type 1, the event-rate at follow-up was significantly higher in the subjects with positive EPS as compared to those with negative EPS (7/35, 20% *vs* 0/43, $p=0.007$); instead, in the patients with drug-induced type 1, the event-rate at follow-up was not statistically different between subjects with positive and negative EPS (2/15, 13% *vs* 0/35, $p=0.16$).

Considering the two groups, in group 1 the event-rate was not statistically different between subjects with positive and negative EPS (2/24, 8% *vs* 0 events, $p=0.21$, Supplementary Material, figure 1A); instead, in group 2 patients with VF induced at EPS

showed a higher incidence of ventricular arrhythmias (7/26, 27% *vs* 0 events in those with negative EPS, p=0.007, Supplementary Material, figure 1B).

In group 1, one arrhythmic event at follow-up occurred in the 14 patients with positive EPS and spontaneous type 1 (7%) and one in the 10 subjects with positive EPS and drug-induced type 1 (p=NS); in group 2, six arrhythmic events occurred in the 21 subjects with positive EPS and spontaneous type 1 (29%) and one in the 5 subjects with positive EPS and drug-induced type 1 (p=NS), Figure 2.

Comparison with the asymptomatic Brugada patients

We finally compared the rate of arrhythmic events at follow-up in group 1 and 2 with the events among the 608 asymptomatic patients from the Brugada Registry. Six patients in the asymptomatic group (1%, 0.2 per 100 person-year) had major arrhythmic events (3 sudden deaths and 3 appropriate ICD shocks). The comparison yielded no statistically significant difference between group 1 and the asymptomatic (p=0.85), whereas the rate of arrhythmic events was significantly higher in group 2 as compare to the asymptomatic (p < 0.001, RR=9; 95%CI: 3-25, figure 1).

Syncopal recurrences at follow-up

In group 1, thirteen patients had recurrence of syncope during the follow-up (11%), 2 had an ICD and 4 an ILR. Syncope was still classified as neurally mediated in all of them, except in one case, described above. In one patient an asystolic pause of 24 seconds was documented by the ILR at the time of syncopal recurrence and an ICD was subsequently implanted, considering the need for pacing. The mean number of recurrences was 1.5±0.7.

In group 2, 8 patients (10%) had recurrence of syncope during follow-up without documented ventricular arrhythmias. The mean number of recurrences was 1.5±1.0. Two of them had an ILR and 5 an ICD. Four of the 5 patients with ICD had undergone EPS, which

had been positive in 3; their average follow-up was 78±32 months. At a retrospective analysis, the syncope of these patients remained unexplained.

Inappropriate shocks

Inappropriate shocks occurred in 5 patients in group 1 (22%) and in 8 patients in group 2 (18%, p=NS). The cause of inappropriate shocks was lead failure in 2, T wave oversensing in one, atrial arrhythmias in 7 and sinus tachycardia in 3 subjects.

Non-sustained VT

Episodes of non-sustained VT (minimum 4 beats) were documented by 12-lead 24-hour Holter recording, ILR or ICD in 8 patients in group 1 (7%) and 12 patients in group 2 (16%), p= NS. The presence of non-sustained VT was associated with a higher incidence of arrhythmic events at follow-up (25% vs 5%, considering only the patients with ICD or ILR, p= 0.03).

Discussion

In this study we have systematically attempted to classify the Brugada patients with syncope into two major clinical entities, neurally mediated (group 1, 118 patients) *v*ersus unexplained, suspected arrhythmia-related syncope (group 2, 77 patients)..

The main finding of our study is that a significant number of syncopal events have an unexplained origin and in this group EPS is the main predictor of life-threatening events. Most syncope in Brugada patients however are neurally mediated and these patients have a prognosis similar to that of the asymptomatic.

Mechanism of syncope in Brugada syndrome

Increases in vagal tone may facilitate the onset of spontaneous ventricular arrhythmias in some patients with Brugada syndrome, thus typical vasovagal symptoms may be observed

in true arrhythmic syncope.[17] Antzelevitch et al.[18] demonstrated, in an experimental model, that acetylcholine-mediated vagal nerve activation shortens the action potential in right ventricular epicardium but not in the endocardium and enhances the ST-segment elevation on the ECG. This effect is rapidly reversed by atropine. Impaired autonomic nervous system in patients with Brugada ECG features may, therefore, represent a common denominator for both neurally mediated syncope and VF.

In 2001 Samniah et al.[19] and Brugada et al.[20] reported two opposite cases with the same initial presentation. In the first, a 30 year-old male had well-documented post-exertional syncope, reproduced during both exercise stress test and HUTT with isoprenaline provocation. He had a drug-induced type 1 Brugada ECG and a single, non-reproducible short run of polymorphic VT at EPS and was treated conservatively, as the syncopal episodes appeared to be neurally mediated. In the second case, a 40-year-old female had recurrent episodes of apparently vasovagal syncope, with positive HUTT, type 1 Brugada ECG after administration of flecainide and VF induced at EPS. An ICD was implanted, which delivered an appropriate shock a few months later. This latter case is similar to our two group 1 patients, described above, who presented with apparent neurally mediated syncope and then had arrhythmic events at follow-up.

Previous studies

Few studies in the Literature dealt with the classification of syncope in Brugada patients and none has clearly assessed the role of the EPS in this subgroup of patients. Take et al.[12] in a group of 84 patients with Brugada ECG and syncope, investigated the characteristics of syncope to differentiate high-risk syncope episodes from low-risk events in patients with Brugada syndrome, demonstrating that syncope with prodromes, especially blurred vision,

suggests a benign etiology of syncope (HR 0.20), while abnormal respiration (HR 2.18) and fragmented QRS (HR 2.39) were independently associated with the occurrence of VF.

In the study by Nordkamp et al,[14] in a group of 118 patients, the features suggesting an arrhythmic origin of the syncopal episodes were male gender, older age, presence of urinary incontinence, absence of typical prodromes and absence of typical triggers. The Authors reported an annual event rate in patients with previous aborted cardiac arrest of 8.7%, while in patients with suspected arrhythmic syncope, the event rate was 2.2% per year, in accordance with our findings. The event rate in patients with unexplained syncope, much lower than that of patients with previous aborted sudden death, was ascribed to a certain number of benign syncope wrongly included in this group.

In the study by Sacher et al,[13] of 57 patients with syncope, 23 (40%) were defined as patients with suspected arrhythmic syncope; they had a rate of ventricular arrhythmias at follow-up of 5.5% per year. In 17 patients (30%) the etiology of syncope remained unclear; they had no arrhythmic events at a mean follow-up of 65 months. The Authors suggested that an ILR should be offered to all patients with syncope of unknown origin.

Characteristics of the two groups

In this study syncope after coughing, micturition, venipuncture, sight of blood, intense pain was present only in group 1. In group 1, patients had a longer mean PR interval as compared to the other group, probably due to a greater vagal activation. Syncope during driving was reported by 10 patients (13%) in group 2 and only by one in group 1 (1%),. The explanation of this finding, which was not reported in the literature so far, remains unknown.

Sensitivity and positive predictive values of each feature of syncope in predicting life-threatening arrhythmias at follow-up resulted relatively low, due to the low number of

events. The most significant variable in identifying patients with events was nocturnal agonal respiration with a positive predictive value of 25%; a positive predictive value greater than 10% was also observed for syncope during driving, syncope in the absence of prodromes/specific situations and during exercise. As we already demonstrated in a previous work,[7] prodromes can precede syncopal episodes of both arrhythmic and neurally mediated origin.

Follow-up

The incidence of arrhythmic events at a mean follow-up of 62 months was 2% (0.3 per 100 person-year) in group 1 (=neurally mediated syncope) and 9% (1.8 per 100 person-year) in group 2 (=unexplained syncope), with a statistically significant difference (p=0.04) and a relative risk of 5.

In group 1, two patients with ICD had syncopal recurrences at follow-up, which were classified as neurally mediated in one case and arrhythmic in the other. In group 2, 5 patients with ICD had syncopal recurrences, all classified as neurally mediated. This finding confirms that the vast majority of syncope in Brugada patients has not an arrhythmic origin.

Spontaneous type 1 ECG had a higher prevalence in the subjects with arrhythmic events, even if not statistically significant, probably due to the low number of events. Moreover, it is well known that spontaneous type 1 may be underestimated, due to the fluctuations of the Brugada ECG pattern.[21,22] The two events in the patients with drug-induced type 1 occurred late, after about 10 year of follow-up: this may be due to a change in the patient ‘s risk profile over time.

Role of electrophysiological study

The best predictor of arrhythmic events at follow-up was VF induction at EPS. This finding

was particularly evident when considering only group 2 patients (27% of events, 5.3 per 100 person-year, Supplementary Material, figure 1B). In group 1, instead, patients with positive EPS did not show a significantly higher incidence of ventricular arrhythmias as compared to those with negative EPS (8%, 1.6 per 100 person-year, Supplementary Material, figure 1A). The association that could best predict the occurrence of ventricular events was the presence of unexplained syncope, spontaneous type 1 and positive EPS (29%, 5.6 per 100 person-year, figure 2). No patients with negative EPS had arrhythmic events at follow-up. Therefore, EPS resulted to be the best tool to identify the patients at higher risk for life-threatening events among those with syncope of unexplained origin. As a consequence, the subjects with VF induced at EPS have the strongest recommendation to ICD implantation. In the study by Sacher et al,[13] none of the 6 subjects with syncope of doubtful origin and ICD experienced arrhythmic events at a 60-month mean follow-up; similarly, in the work by Nordkamp et al,[14] the patients with suspected arrhythmic syncope had a lower rate of events at follow-up as compared to the patients with cardiac arrest. We believe that EPS may be of help to further stratify the risk of patients with unexplained syncope, considering the number of benign syncope wrongly included in this group, and to avoid unnecessary ICD implantations. In our study, the 13 patients of group 2 with a negative EPS and spontaneous type 1 ECG, who did not received an ICD, had no arrhythmic events at a mean follow-up of 47±40 months. In the Literature, the role of programmed electrical stimulation in the risk stratification of Brugada patients remains controversial.[4-9,23] However, data from a recent meta-analysis confirm the prognostic value of a positive EPS.[24]

ICD and implantable loop-recorder

When dealing with the decision of implanting an ICD, two things should be taken in mind.

The first is the non-negligible rate of ICD-related complications; the second is that appropriate ICD shocks should not be considered synonymous of sudden death, as ventricular tachyarrhythmias might also terminate spontaneously.[8] In our study, the events at follow-up were always ventricular arrhythmias interrupted by ICD shock, therefore, the risk of life-threatening events could have been overestimated. However, asymptomatic episodes of non-sustained VT detected by 24-hour Holter recording, ILR or ICD were associated with a significantly higher risk of arrhythmic events at follow-up. Moreover, the role of implantable loop recorder (ILR) was important in our experience, as it allowed a better etiological definition of syncopal episodes. A more extensive use of the ILR in subjects with unexplained syncope with negative EPS and in those with neurally mediated syncope and spontaneous type 1 might be suggested.

In this study, group 1 patients had a prognosis comparable to that of the asymptomatic subjects of the Registry (0.2 events per 100 person years). In our Center, EPS is currently proposed in group 1 only in presence of spontaneous type 1 ECG. EPS has a predominant role in group 2 patients, both with spontaneous type 1 or not, and, in case of positive EPS, ICD implantation is strongly indicated.

Conclusions

Etiological definition of syncopal episodes in Brugada patients is important, as it allows identifying two groups with different outcome. Patients with unexplained syncope have a significantly higher risk of arrhythmic events at follow-up and EPS is particularly useful in this group, to identify the patients with the strongest indication to ICD implant. Patients presenting with neurally mediated syncope show a prognosis similar to that of the asymptomatic and the role of EPS in this group, even in the presence of spontaneous type

1, is unproven.

Funding sources: none.

Conflict of interest: none declared.

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Figure legends

Figure 1. Kaplan Meier curves for the probability of freedom from arrhythmic events for the two cohorts (neurally mediate vs unexplained syncope) and for the asymptomatic Brugada patients of the Piedmont Registry. The curve of group 1 is significantly different form the curve for group 2, while substantially overlaps the curve for the asymptomatic patients.

Figure 2. Event rates at follow-up. Incidence of arrhythmic events in the 2 groups in relation to VF inducibility at EPS, considering only patients with spontaneous type 1 ECG. EPS= electrophysiological study; f-up= mean follow up in months; ICD= implantable cardioverter defibrillator.

Supplementary Material, figure 1A and 1B. Kaplan Meier curves for the probability of freedom from arrhythmic events for patients with positive and negative EPS in group 1 and 2.

Table 1 A. Characteristics of patients in the 2 groups (G1= neurally mediated syncope; G2= unexplained syncope).

	G1	G2
Number	118/195 (60%)	77/195 (40%)
Age at diagnosis (years)	45±13	44±14
Age at 1st syncope	33±16	36±15
Total number of syncope	2.1±1.5	1.2±0.8
Men	83/118 (70%)	63/77 (82%)
Spontaneous type 1 ECG	46/118 (39%)	51/77 (66%)
Family history of SD at age <45 years	12/118 (10%)	16/77 (21%)
Genetic test	42/118 (36%)	41/77 (54%)
SCN5A/SCN1B mutation	15/42 (36%)	11/41 (27%)
PR interval (ms)	185±30	169±29
Supraventricular arrhythmias	12/118 (10%)	7/77 (9%)
Tilt test	27/118 (23%)	10/77 (13%)
Positive tilt test	12/27 (44%)	1/10 (10%)
EPS	71/118 (60%)	57/77 (74%)
Positive EPS	24/71 (34%)	26/57 (46%)
Hydroquinidine	12/118 (10%)	10/77 (13%)
Loop recorder	13/118 (11%)	14/77 (18%)
ICD	23/118 (19%)	44/77 (57%)
Documented NSVT	8/38 (21%)	12/56 (21%)
Mean follow-up (months)	58±46	67±42
Events at follow-up	2/118 (2%)	7/77 (9%)

EPS= electrophysiological study; ICD= implantable cardioverter defibrillator; NSVT= non-sustained ventricular tachycardia; SD= sudden death.

Table 1 B. Characteristics of syncope in the 2 groups (G1= neurally mediated syncope; G2= suspected arrhythmic syncope).

	G1 **n=118**	**G2** **n=77**
Prodromes (nausea, vomiting, diaphoresis, pallor, flushing, dizziness, blurred vision, scotoma, weakness, palpitations, dyspnea)	78/86† (91%)	30/76† (40%)
Fever	16/118 (14%)	12/77 (16%)
Standing position or during postural changes	62/99† (63%)	26/61† (43%)
Sitting position	32/99† (32%)	27/61† (44%)
Supine position	5/99† (5%)	8/61† (13%)
During exercise	1/118 (1%)	5/77 (7%)
After exercise	4/118 (3%)	3/77 (4%)
After strong emotion/ stress/trauma	16/118 (14%)	5/77 (7%)
After coughing, micturition, defecation, venipuncture, seeing blood, intense pain	47/118 (40%)	0/77
After meal/drink	15/118 (13%)	17/77 (22%)
During driving	1/118 (1%)	10/77 (13%)
Hot places	10/118 (8%)	4/77 (5%)
During gastroenteritis	5/118 (4%)	1/77 (1%)
Convulsion, morsus	3/118 (3%)	7/77 (9%)
Incontinence	3/118 (3%)	6/77 (8%)
Agonal respiration	0/118	4/77 (5%)
With trauma	10/118 (8%)	18/77 (24%)
Contraindicated drugs, alcohol	2/118 (2%)	3/77 (4%)
Hypotensive drugs	2/118 (2%)	2/77 (3%)

†Denominator refers to the number of patients in whom the data was available.

Table 2. Characteristics of patients with and without major arrhythmic events at follow-up in the two groups.

	Group 1 (neurally mediated)			Group 2 (unexplained)		
	events	**No events**	**p- value**	**events**	**No events**	**p- value**
Number	2	116	-	7	70	-
Age at diagnosis (years)	41±13	45±13	NS	41±13	44±15	NS
Males	2 (100%)	81 (70%)	NS	6 (86%)	57 (81%)	NS
Spontaneous type 1 ECG	1(50%)	45 (39%)	NS	6 (86%)	45 (64%)	NS
Family history of SD at age <45 years	0	12 (10%)	NS	1 (14%)	15 (21%)	NS
Genetic testing	1 (50%)	41 (35%%)	NS	6 (86%)	35 (50%)	NS
Mutation (SCN5A/SCN1B)	0	15 (36%)	NS	3 (43%)	8 (23%)	NS
PR interval (ms)	160	185±30	NA	188±30	166±30	NS
Supraventricular arrhythmias	0	12 (10%)	NS	3 (43%)	4 (6%)	0.01
Tilt test	2 (100%)	25 (22%)	NS	2 (29%)	8 (11%)	NS
Positive tilt test	1 (50%)	11 (44%)	NS	1 (14%)	0	NS
EPS	2 (100%)	69 (60%)	NS	7 (100%)	50 (71%)	NS
Positive EPS	2 (100%)	22 (32%)	NS	7 (100%)	19 (38%)	0.007
Loop recorder	0	13 (11%)	NS	0	14 (20%)	NS
ICD	2 (100%)	21 (18%)	0.05	7 (100%)	37 (74%)	0.05
Documented NSVT in patients with ICD or loop recorder	1 (50%)	7 (6%)	NS	4 (57%)	8 (11%)	0.008
Mean follow-up (months)	56±74	55±47	NS	41±38	64±43	NS

EPS= electrophysiological study; ICD= implantable cardioverter defibrillator; NSVT= non-sustained ventricular tachycardia; SD= sudden death. NS= non significant; NA= not applicable.